Phosphodiesterase type 5 inhibitors and risk of melanoma: A meta-analysis

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Background: The association between phosphodiesterase type 5 (PDE5) inhibitors and melanoma risk is controversial.

Objective: We quantify the association between use of PDE5 inhibitors and melanoma.

Methods: We systematically searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov for studies that were conducted up to July 13, 2016, and evaluated the association between PDE5 inhibitors and skin cancer. Random effects meta-analyses were used to calculate the adjusted odds ratio (OR) with the 95% confidence interval (CI).

Results: Five observational studies were included. Compared with PDE5 inhibitor nonuse, PDE5 inhibitor use was slightly but significantly associated with an increased risk for development of melanoma (OR, 1.12; 95% CI, 1.03-1.21) and basal cell carcinoma (OR, 1.14; 95% CI, 1.09-1.19) but not squamous cell carcinoma. For melanoma risk, none of the prespecified factors (dose of PDE5 inhibitor, study design, and study region) significantly affected the results ($P > .05$). Our sensitivity analysis confirmed the stability of the results.

Limitations: We included only observational studies, which had some heterogeneities and inconsistent controlling for potential confounders.

Conclusions: Use of PDE5 inhibitors may be associated with a slightly increased risk for development of melanoma and basal cell carcinoma but not squamous cell carcinoma. However, further large well-conducted prospective studies with adequate adjustment for potential confounders are required for confirmation. (J Am Acad Dermatol 2017;77:480-8.)

Key words: basal cell carcinoma; melanoma; meta-analysis; PDE5 inhibitor; squamous cell carcinoma.

Phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil, tadalafil, and vardenafil inhibit cyclic guanosine-3′,5′-monophosphate (cGMP)-degrading PDE5 in the vascular smooth muscle and are widely used treat erectile dysfunction.[1] Interestingly, activation of this cGMP pathway has been shown to promote melanoma cell growth and migration,[2,3] and this link has recently been confirmed.[4] These laboratory observations

Abbreviations used:

BCC:	basal cell carcinoma
cGMP:	cyclic guanosine-3′,5′-monophosphate
CI:	confidence interval
NOS:	Newcastle-Ottawa quality-assessment scale
OR:	odds ratio
PDE5:	phosphodiesterase type 5
SCC:	squamous cell carcinoma

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have prompted several observational studies assessing the association between PDE5 inhibitors and risk for development of melanoma.[5-9]

In 2014, the first cohort study on this subject (Li et al) among a United States–based cohort of male health professionals indicated that self-reported use of PDE5 inhibitors was significantly associated with higher risk for development of melanoma compared with nonuse.[5] However, their results were based on only 142 patients with melanoma, of whom 14 used sildenafil. Since the article by Li et al, 4 additional studies have been published. A nested case-control study (Loeb et al [2015]) suggested a modest association between PDE5 inhibitors and risk for development of melanoma but did not meet several of Hill's causality criteria.[6] However, 2 epidemiologic studies indicated no association.[7,9] Given these inconsistencies among individual studies, it is not possible to determine whether there is a link between PDE5 inhibitors and risk for development of melanoma.

CAPSULE SUMMARY

- Previous studies have reported conflicting results on possible associations between use of phosphodiesterase type 5 (PDE5) inhibitors and the risk for development of melanoma.
- This meta-analysis of 5 observational studies suggested a slight but significant association between PDE5 inhibitors and both melanoma and basal cell carcinoma, with some evidence of heterogeneity.
- There were several limitations of this study, and future well-conducted prospective studies are warranted to assess the modest association.

PDE5 inhibitors are an effective intervention and are recommended as first-line treatment for erectile dysfunction, which affects more than 18 million men in the United States, or up to 20% of men age 20 years or older.[10] With the expiration of the patents on sildenafil and other PDE5-inhibiting drugs, lower costs and more direct-to-consumer advertising will certainly increase the number of users. Understanding the possible connections between PDE5 inhibitors and the incidence of melanoma is an important public health issue.

We therefore conducted a study-level meta-analysis of available evidence from observational studies to quantify the possible association between use of PDE5 inhibitors and risk for development of skin cancers. No randomized trials on this association were available. We also performed a cumulative meta-analysis and sensitivity analysis to assess the robustness of the results from the available studies.

METHODS

Search strategy and study selection

We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov to identify randomized trials or observational studies that had been published up to July 13, 2016, and evaluated the association between exposure to PDE5 inhibitors and risk for development of skin cancer. We searched for a combination of the terms *sildenafil* or *vardenadil* or *avanafil* or *tadalafil* or *phosphodiesterase type 5* or *phosphodieterase-5* or *PDE5* and *melanoma* or *basal cell carcinoma* or *squamous cell carcinoma* or *skin cancer* without any restriction. We selected the studies according to the following inclusion criteria: (1) randomized controlled trials, cohort studies, or case-control studies; (2) studies comparing PDE5 inhibitors with placebo or non-PDE5 inhibitors; (3) follow-up for at least 52 weeks (not applicable to case-control studies), because little information relevant to cancer incidence was reported in studies of shorter duration; and (4) reporting of the outcomes of skin cancer. The primary outcome of interest was risk for development of melanoma, and secondary outcomes included basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). We excluded conference abstracts because they offer limited information with which to assess study quality, population, and outcomes.

Data extraction and quality assessment

We collected information on study design, drug use, study location, characteristics of participants, selection criteria, definition of *exposure*, adjusted covariates, and outcomes of interest. Data on outcomes such as adjusted hazard ratio, adjusted risk ratio, and adjusted odds ratio (OR) were extracted if appropriate. The Cochrane risk of bias tool for randomized trials[11] and the Newcastle-Ottawa scale (NOS) for observational studies[12] were used to assess quality. For NOS criteria, a maximum of 9 stars would be allocated to the following domains: selection, comparability, and outcome/exposure, with higher scores indicating better quality. Two reviewers (H.T. and W.W.) independently extracted the data and assessed the quality of each study. Any disagreements were resolved by consensus or referral to a third reviewer (J.H.).